

CLAIMS:

1. A pharmaceutical formulation comprising an active agent selected from the group consisting of a monoaminopyridine and a diaminopyridine for administration on a once- or twice-daily basis, said formulation including said mono- or di-aminopyridine active agent in a carrier effective to permit release of said mono- or di-aminopyridine at a rate allowing controlled absorption thereof over, on the average, not less than a 12 hour period and at a rate sufficient to achieve therapeutically effective blood levels over a period of 12-24 hours following administration.
2. A pharmaceutical formulation according to Claim 1, which comprises a pellet for oral administration, said pellet comprising a core of an active agent selected from the group consisting of a monoaminopyridine, a diaminopyridine and pharmaceutically acceptable salts thereof in association with one or more pharmaceutically acceptable excipient(s), the mono- or di-aminopyridine component and the pharmaceutically acceptable excipient(s) being present in a ratio of from 10:1 to 1:20, and a multi-layer membrane surrounding said core and containing a major proportion of a pharmaceutically acceptable film-forming, water insoluble polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water soluble polymer, the number of layers in said membrane and the ratio of said water soluble to water insoluble polymer, when said water soluble polymer is present, being effective to permit release of said mono- or di-aminopyridine from said pellet at a rate allowing controlled absorption thereof over, on the average, not less than a 12 hour period following oral administration, said rate being measured *in vitro* as a dissolution rate of said pellet, which when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at 50 r.p.m. substantially corresponds to the following:
- a) no more than 50% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

- b) no more than 75% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus; and
- 5 c) 100% of the mono- or di-aminopyridine is released no earlier than after 8 hours of measurement in said apparatus.

10 3. A pharmaceutical formulation according to Claim 2, wherein the release of mono- or di-aminopyridine from said pellet is at a rate allowing controlled absorption thereof over a 24 hour period following oral administration, said rate being measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at 50 r.p.m. which substantially corresponds to the following dissolution pattern:

- 15 a) from 0 to 40% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;
- b) from 20 to 60% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;
- c) from 30 to 80% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus;
- 20 d) from 50 to 90% of the total mono- or di-aminopyridine is released after 12 hours of measurement in said apparatus; and
- e) not less than 75% of the total mono- or di-aminopyridine is released after 24 hours of measurement in said apparatus.

25 4. A pharmaceutical formulation according to Claim 2, wherein the release of mono- or di-aminopyridine from said pellet is at a rate allowing controlled absorption thereof over a 12 hour period following oral administration, said rate being measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at

50 r.p.m. which substantially corresponds to the following dissolution pattern:

- a) from 0 to 40% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;
- 5 b) from 20 to 60% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;
- c) from 30 to 80% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus; and
- 10 d) not less than 75% of the total is released after 12 hours of measurement in said apparatus.

5. A pharmaceutical formulation according to Claim 2 or 3 or 4, wherein the core comprises:

- 15 a) a powder mixture containing a mono- or di-aminopyridine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, and
- b) a polymeric material containing a major proportion of a pharmaceutically acceptable water soluble polymer and a minor proportion of a pharmaceutically acceptable water insoluble polymer,

20 said core comprising layers of said powder mixture and said polymeric material superimposed one upon the other and said polymeric material being present in an amount effective to ensure that all of said powder mixture is coated into said core.

- 25 6. A pharmaceutical formulation according to Claim 2 or 3 or 4, wherein the water soluble polymer in the core or membrane is the same or different and is selected from the group consisting of polyvinyl

alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, agar, carrageenan, xanthan and polyethylene glycol and mixtures thereof.

7. A pharmaceutical formulation according to Claim 2 or 3 or  
5 4, wherein the water soluble polymer in the core or membrane is replaced by a polymeric material which is freely permeable to mono- or di-aminopyridine and water and comprises a copolymer of acrylic and methacrylic acid esters.

8. A pharmaceutical formulation according to Claim 2 or 3 or  
10 4, wherein the water insoluble polymer in the core or membrane is selected from the group consisting of ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(ethylene) low density, poly(ethylene)  
15 high density, poly(propylene), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride) and polyurethane and mixtures thereof.

9. A pharmaceutical formulation according to Claim 2 or 3 or  
20 4, wherein the water insoluble polymer of the core or membrane is selected from a naturally occurring polymer selected from the group consisting of shellac, chitosan and gum juniper and mixtures thereof.

10. A pharmaceutical formulation according to Claim 2 or 3 or  
25 4, wherein the water insoluble polymer in the core or membrane is replaced by a polymeric material which is slightly permeable to mono- or di-aminopyridine and water and comprises a copolymer of acrylic and methacrylic acid esters.

11. A pharmaceutical formulation according to Claim 2 or 3 or 4, wherein the mono- or di-aminopyridine, pharmaceutically acceptable excipient(s) and polymeric material are built up on an inert core.
12. A pharmaceutical formulation according to Claim 2 or 3 or 5 4, wherein the mono- or di-aminopyridine, pharmaceutically acceptable excipient(s) and polymeric material are built up on a nonpareil seed of sugar/starch having an average diameter in the range 0.2 - 1.4 mm.
13. A pharmaceutical formulation according to Claim 2 or 3 or 10 4, wherein the mono- or di-aminopyridine, pharmaceutically acceptable excipient(s) and polymeric material are built up on a central active core.
14. A pharmaceutical formulation according to Claim 2 or 3 or 15 4, wherein the mono- or di-aminopyridine, pharmaceutically acceptable excipient(s) and polymeric material are built up on a central active core formed by blending the mono- or di-aminopyridine, pharmaceutically acceptable excipient(s) and polymeric material to form a homogeneous powder, shaping a portion of said blend to form a central core and applying the remainder of said blend alternately or simultaneously with a polymer binding solution to form a layered structure on said central core.
- 20 15. A pharmaceutical formulation according to Claim 2 or 3 or 4, wherein the mono- or di-aminopyridine, pharmaceutically acceptable excipient(s) and polymeric material are built up on a central active core formed by blending the mono- or di-aminopyridine, pharmaceutically acceptable excipient(s) and polymeric material to form a homogeneous powder, shaping a portion of said blend to form a central core and applying the remainder of said blend alternately or simultaneously with a polymer binding solution to form a layered structure on said central core and the completed cores have an average diameter in the range 0.4 - 1.6 mm.
- 25 30 16. A controlled absorption mono- or di-aminopyridine formulation for oral administration, comprising pellets according to

Claim 2 or 3 or 4, said formulation including a sufficient quantity of a rapid release form of mono- or di-aminopyridine to ensure prompt achievement of therapeutically effective blood levels together with therapeutically effective blood levels over a 12 to 24 hour period

5 following each oral administration.

17. A controlled absorption mono- or di-aminopyridine formulation for oral administration, comprising pellets according to Claim 2 or 3 or 4 and a sufficient quantity of a rapid release form of a mono- or di-aminopyridine to ensure prompt achievement of 10 therapeutically effective blood levels together with therapeutically effective blood levels over a 12 to 24 hour period following each oral administration, said formulation having a dissolution rate which when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at 50 r.p.m. substantially corresponds to 15 the following dissolution pattern:

- a) from 20 to 60% of the total mono- or di-aminopyridine is released after 2 hours of measurement in said apparatus;
- b) from 30 to 70% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;
- c) from 50 to 90% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus; and
- d) not less than 75% of the total mono- or di-aminopyridine is released after 12 hours of measurement in said apparatus.

25 18. A controlled absorption mono- or di-aminopyridine formulation for oral administration, comprising pellets according to Claim 2 or 3 and a sufficient quantity of a rapid release form of a mono- or di-aminopyridine to ensure prompt achievement of 30 therapeutically effective blood levels together with therapeutically effective blood levels over a 24 hour period following each oral administration, said formulation having a dissolution rate which when measured in a type II dissolution apparatus according to U.S.

Pharmacopoeia XXII in water and at 50 r.p.m. substantially corresponds to the following dissolution pattern:

- a) from 10 to 40% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;
- 5 b) from 25 to 65% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;
- c) from 40 to 80% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus;
- 10 d) from 50 to 90% of the total mono- or di-aminopyridine is released after 12 hours of measurement in said apparatus;  
and
- e) not less than 75% of the total mono- or di-aminopyridine is released after 24 hours of measurement in said apparatus.

19. A controlled absorption mono- or di-aminopyridine formulation for oral administration, comprising pellets according to Claim 2 or 4 and a sufficient quantity of a rapid release form of a mono- or di-aminopyridine to ensure prompt achievement of therapeutically effective blood levels together with therapeutically effective blood levels over a 12 hour period following each oral administration, said formulation having a dissolution rate which when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water and at 50 r.p.m. substantially corresponds to the following dissolution pattern:

- 25 a) from 20 to 50% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;
- b) from 30 to 70% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;

- c) from 40 to 80% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus; and
- d) not less than 75% of the total mono- or di-aminopyridine is released after 12 hours in said apparatus.

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20. A controlled absorption mono- or di-aminopyridine formulation, which comprises a blend of pellets according to Claim 2 or 3 or 4, together with up to 60% by weight of a rapid release form of mono- or di-aminopyridine.

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21. A controlled absorption mono- or di-aminopyridine formulation according to Claim 2 or 3 or 4, together with up to 60% by weight of rapid release pellets of a mono- or di-aminopyridine.

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22. A controlled absorption mono- or di-aminopyridine formulation according to Claim 2 or 3 or 4, together with up to 60% by weight of rapid release pellets of a mono- or di-aminopyridine, said rapid release pellets comprising a core of an active agent selected from the group consisting of a monoaminopyridine, a diaminopyridine and pharmaceutically acceptable salts thereof in association with one or more pharmaceutically acceptable excipient(s), the mono- or di-aminopyridine component and the pharmaceutically acceptable excipient(s) being present in a ratio of from 10:1 to 1:20 and a multi-layer membrane surrounding said core and containing a major proportion of a pharmaceutically acceptable film-forming, water soluble polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water insoluble polymer, the number of layers in said membrane and the ratio of said water soluble to water insoluble polymer being effective to allow relatively immediate release of the active agent from said pellet.

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23. A controlled absorption mono- or di-aminopyridine formulation according to Claim 2 or 3 or 4, together with up to 60% by weight of rapid release pellets of a mono- or di-aminopyridine, said

- rapid release pellets comprising a core of an active agent selected from the group consisting of a monoaminopyridine, a diaminopyridine and pharmaceutically acceptable salts thereof in association with one or more pharmaceutically acceptable excipient(s), the mono- or di-  
5 aminopyridine component and the pharmaceutically acceptable excipient(s) being present in a ratio of from 10:1 to 1:20 and a multi-layer membrane surrounding said core and containing a major proportion of a pharmaceutically acceptable film-forming, water soluble polymer and optionally a minor proportion of a  
10 pharmaceutically acceptable film-forming, water insoluble polymer, the number of layers in said membrane and the ratio of said water soluble to water insoluble polymer being effective to allow relatively immediate release of the active agent from said pellet, said rapid release pellets having a dissolution rate, which when measured *in vitro* in a type II  
15 dissolution apparatus according to US Pharmacopoeia XXII in water at 50 r.p.m. substantially corresponds to the following dissolution pattern:
- (a) not less than 70% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus; and  
20 (b) not less than 85% of the total mono- or di-aminopyridine is released after 2 hours of measurement in said apparatus.
24. A formulation according to Claim 1 or 2 or 3 or 4, from which the mono- or di-aminopyridine active agent is released at a rate allowing controlled absorption thereof over a twenty-four hour period following oral administration, said rate being measured *in vivo* and  
25 having a Tmax between 2 and 16 hours and achieving minimum effective blood levels from 12 to 20 hours over a 24 hour period.  
30 25. A pharmaceutical formulation according to Claim 1 for the once-daily, percutaneous administration of a mono- or di-aminopyridine active agent, which formulation comprises said mono- or di-aminopyridine uniformly distributed in a solid, semi-solid or mucilaginous medium which can be placed in intimate contact with the skin, the release of said mono- or di-aminopyridine from said

formulation being at a rate sufficient to achieve therapeutically effective blood levels over a period of 12 to 24 hours following topical application of said formulation.

26. A pharmaceutical formulation according to Claim 1 for the  
5 once-daily, percutaneous administration of a mono- or di-aminopyridine active agent, which formulation comprises said mono- or di-aminopyridine uniformly distributed in a solid, semi-solid or mucilaginous medium which can be placed in intimate contact with the skin, the release of said mono- or di-aminopyridine from said  
10 formulation being at a rate allowing controlled absorption thereof over a 24 hour period following topical application of said preparation, said rate being measured *in vivo* and having a Tmax between 2 and 16 hours.

27. A pharmaceutical formulation according to Claim 25 or 26,  
15 which contains from 10-100 mg of active agent.

28. A pharmaceutical formulation according to Claim 25 or 26, which contains from 25-75 mg of active agent.

29. A pharmaceutical formulation according to Claim 25 or 26,  
20 wherein the solid, semi-solid or mucilaginous medium comprises a gum selected from the group consisting of guar gum, acacia gum, ghatti gum, karaya gum, tragacanth gum, xanthan gum and mixtures thereof.

30. A pharmaceutical formulation according to Claim 25 or 26,  
25 wherein the solid, semi-solid or mucilaginous medium comprises a synthetic or natural polysaccharide selected from the group consisting of alkylcelluloses, hydroxyalkylcelluloses, cellulose ethers, cellulose esters, nitrocelluloses, dextrin, agar, carrageenan, pectin, furcellaran and starch and starch derivatives and mixtures thereof.

31. A pharmaceutical formulation according to Claim 25 or 26,  
wherein the solid, semi-solid or mucilaginous medium comprises a

polypeptide selected from the group consisting of zein, gelatin, collagen, polygeline and mixtures thereof.

32. A pharmaceutical formulation according to Claim 25 or 26, wherein the solid, semi-solid or mucilaginous medium comprises an alginate selected from the group consisting of alginic acid, propylene glycol alginate, sodium alginate and mixtures thereof.

33. A pharmaceutical formulation according to Claim 25 or 26, which includes one or more auxiliary agent(s) selected from the group consisting of an antimicrobial agent, a preservative, an antioxidant, a pH-controlling agent, a plasticizer, a surfactant, a penetration enhancer, a humectant, a local anaesthetic, an anti-irritant agent, rubefacient and mixtures thereof.

34. A capsule comprising pellets according to Claim 2 or 3 or 4.

35. A tablet formulation comprising pellets according to Claim 2 or 3 or 4.

36. A pharmaceutical formulation according to Claim 2 or 3 or 4, wherein the active agent is a mono-aminopyridine.

37. A pharmaceutical formulation according to Claim 2 or 3 or 4, wherein the mono-aminopyridine is 4-aminopyridine.

38. A method for the treatment of a neurological disease characterised by a slowing of nerve impulse transmission, which comprises administering to a patient a medicament containing a mono- or di-aminopyridine active agent, said medicament being effective to permit release of said active agent in a manner which achieves therapeutically effective blood levels over a 12-24 hour period when administered on a once- or twice-daily basis.

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2 30. A method according to Claim 28, wherein the neurological disease is characterised by demyelination of the central nervous system.

B 3 40. A method according to Claim 38 or 39, wherein the neurological disease is multiple sclerosis.

5 4 41. A method according to Claim 38, wherein the neurological disease is Alzheimer's disease.

6 5 42. A method according to Claim 38, wherein the medicament is administered to a subject at a dose and for a period sufficient to allow said subject to tolerate said dose without showing any adverse effects and thereafter increasing the dose of <sup>mono- or di-aminopyridine</sup> active agent at selected intervals of time until a therapeutic dose is achieved.

4 43. A method according to Claim 42, wherein at the commencement of treatment the <sup>mono- or di-aminopyridine</sup> active agent is administered at a dose of less than 15 mg/day until a tolerable state is reached.

7 15 44. A method according to Claim 42, wherein at the commencement of treatment the <sup>mono- or di-aminopyridine</sup> active agent is administered at a dose of less than 15 mg/day until a tolerable state is reached and when said tolerable state is reached, the dose administered is increased by amounts of at least 5-15 mg/day until said therapeutic dose is reached.

8 20 45. A method according to Claims 38, wherein the active agent is 4-aminopyridine.

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